American Journal of Medical Genetics 70:421–426 (1997)

Pattern of Malformations in the Axial Skeleton in Human Trisomy 13 Fetuses

Inger Kjær,[1]* Jean W. Keeling,[2] and Birgit Fischer Hansen[3]

[1]*Department of Orthodontics, School of Dentistry, University of Copenhagen, Copenhagen, Denmark*
[2]*Department of Pathology and Cytogenetics, Royal Hospital for Sick Children, Edinburgh, Scotland*
[3]*Department of Pathology, Hvidovre University Hospital, Hvidovre, Denmark*

The purpose of this study was to analyse the development of the axial skeleton in human trisomy 13 fetuses and to define which fields in the axial skeleton are affected in this condition.

We investigated nine human fetuses with trisomy 13 and gestational ages of 14–19 weeks. Whole body radiographs and radiographs of midsagittal tissue blocks of the cranial base and the spine were studied. In the youngest fetus, 14 w GA, no malformations were observed.

In eight fetuses, 17–19 weeks GA, malformations occurred in the lumbosacral spine. In four fetuses additional malformations were observed in the thoracic spine. The study showed that there was a correspondence between the extent of malformation in the lumbosacral spine and the thoracic spine. When mild malformation occurred in the lumbosacral region, no malformation was observed in the thoracic region, whereas malformation was observed in the thoracic region when there was extensive malformation in the lumbosacral region.

Malformations did not occur in the cervical spine or the basilar part of the occipital bone, but the postsphenoidal part of the sphenoid bone was small and irregular in the six cases where it could be examined. In seven fetuses there was malformation or agenesis of the nasal bone.

This pattern of axial skeletal malformations in trisomy 13 fetuses was not described previously. Comparisons are made with previous studies of the fetal axial skeleton in trisomy 18 and trisomy 21, where the pattern of malformations was different. We reiterate our recommendation that axial skeletal radiography should be part of the postmortem examination of fetuses with suspected or verified chromosome abnormalities. Am. J. Med. Genet. 70:421–426, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: **vertebra; cranial base; nasal bone; radiography; notochord; chromosome**

INTRODUCTION

Investigation of the fetal axial skeleton in trisomy 18 and trisomy 21 showed that different fields were affected [Kjær et al., 1996; Keeling et al., 1997]. Therefore it seemed appropriate to investigate the axial skeleton in trisomy 13.

In studies of the skeletal phenotype in trisomy 13 the anomalies most commonly described are wide anterior fontanelle, presence of a cervical rib, absence of the 12th rib, anomalies of rib morphology, low acetabular angles, and long distal phalanges [Patau et al., 1960; Mottet and Jensen, 1965; Snodgrass et al. 1966; Taylor, 1968; Colacino and Pettersen, 1978; Pettersen et al., 1979; Jacobs et al., 1987; Keeling, 1994]. Malformations of the fifth finger and toe are frequent, and polydactyly has also been reported [Opitz et al., 1979; Gilbert and Opitz, 1982]. In cases with holoprosencephaly, a range of malformations in the cranial bones has been observed [Kjær et al., 1991].

The axial skeleton in trisomy 13 has not, hitherto, been examined in detail.

MATERIALS AND METHODS

Material

Nine human fetuses (five males and four females) with trisomy 13, gestational ages 14 to 19 weeks, were included in the study. Deficient neural tube closure was not present.

The fetuses were examined with parental consent at the Royal Hospital for Sick Children, Edinburgh, Scot-

Contract grant sponsor: Vera and Carl Johan Michaelsen's Foundation; Contract grant sponsor: Danish Medical Research Council; Contract grant number: 9401187.

*Correspondence to: Inger Kjær, Department of Orthodontics, School of Dentistry, Faculty of Health Sciences, University of Copenhagen, 20 Nørre Allé, DK-2200 Copenhagen N, Denmark.

Received 8 July 1996; Accepted 25 November 1996

land, and at the Hvidovre University Hospital, Denmark.

Methods

Whole body radiographs in frontal and lateral projections were taken. In six cases this was followed by dissection and further radiological analysis. By dissection, a midsagittal block of the cranial base and the entire spine was isolated by two sagittal incisions at the lateral border of the foramen magnum, continuing along the lateral aspects of the entire spine [Kjær, 1990a,b; Kjær et al., 1993; Kjær, 1994]. The midsagittal segment was radiographed in frontal and lateral projections.

Radiographs of fetal hands and feet were used for skeletal maturity assessment [Kjær, 1974]. Using these standard measurements, standards for the timing and sequence of normal axial skeletal development were calculated and used as a basis for comparison in individual cases [Kjær, 1990a,b; Kjær et al., 1993; Kyrkanides et al., 1993; Sandickioglu et al., 1994]. A Grenz Ray radiographic apparatus (Hewlett Packard Faxitron Series 43805N) was used with Kodak X-Omat MA film. The tissue was placed directly on the film envelope. Depending on the size of the specimen, the tube voltage varied between 20 and 60 kV and the exposure time between 10 and 60 sec at 2.8 to 3.0 mA.

The following seven osseous regions (fields) of the six dissected axial skeletons illustrated in Figure 1 were analysed separately: sacral, lumbar, thoracic, and cervical vertebral segments of the spine, the basilar part of the occipital bone, the postsphenoid component of the sphenoid bone, and the nasal bones.

From the whole body radiographs of the additional three fetuses only the lumbar and nasal fields were investigated.

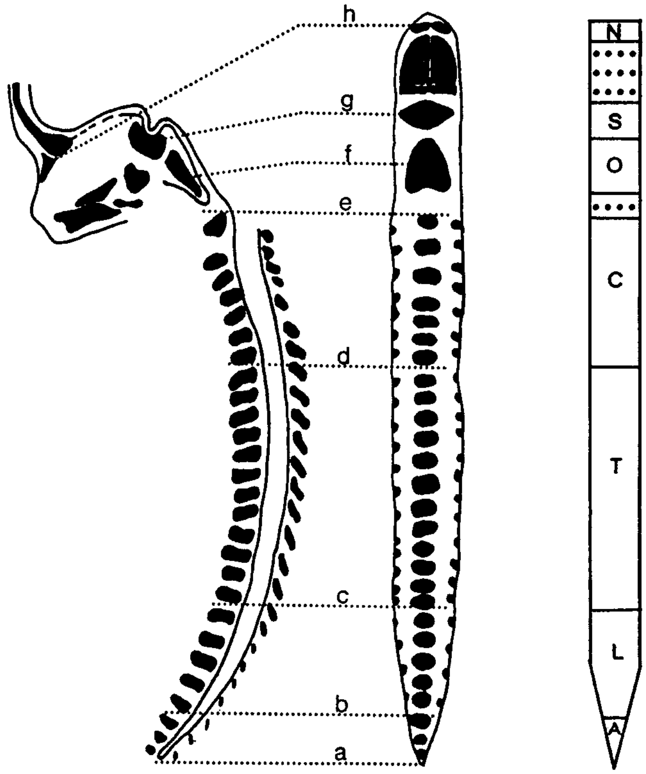

Fig. 1. Drawing of the axial skeleton from a human fetus, 16 w GA, in lateral view (left) and frontal view (centre). The lines a–h indicate the axial developmental fields, marked schematically in the frontal view (right). The coccygeal field between lines a and b is marked A, the lumbar field between lines b and c by L, the thoracic field between lines c and d by T, and the cervical field between lines d and e by C. The basilar part of the occipital bone, indicated by f, is marked O, the postsphenoid bone, indicated by g, is marked S, and the nasal bones, indicated by h, are marked N [Kjær et al., 1996].

RESULTS

The smallest fetus, 14 weeks GA, was skeletally immature and the faint traces of mineralization corresponded to findings in normal fetuses. This fetus, of which only whole body radiographs existed, was not included in the subsequent description, which consequently comprises the skeletal findings in 8 trisomy 13 subjects, 17–19 weeks GA.

Spine

Lumbosacral region. Malformations occurred in all eight fetuses in the lumbosacral region. These were partial vertical clefting of the vertebral bodies in lateral projection, either of a few (Figs. 2–4) or of all vertebral bodies (Figs. 5, 6). The clefting could be either a cleft in the cranial body surface, a cleft in the caudal body surface, or a cranial and a caudal cleft of the vertebral body.

Thoracic region. Malformations were seen in the thoracic region in four axial skeletons of the six examined (Figs. 5, 6). The malformations were partial or complete clefting of the vertebral bodies. Absence of the dorsal segment of the vertebral body was also observed.

The study showed that there was a correspondence between the number of malformed bodies and the degree of malformation of the individual bodies in the lumbar region and the extent of malformation in the thoracic region (Table I). When mild malformation occurred in the lumbosacral region, normal thoracic vertebral bodies were seen. However, when there was more extensive malformation in the lumbosacral field, it was accompanied by malformation in the thoracic field.

Cervical region. Malformations were not observed in the cervical regions.

Cranial Base

Basilar part of the occipital bone. There were no malformations in the six axial skeletons investigated.

Postsphenoid component of the sphenoid bone. Morphological abnormalities were seen in all six axial skeletons investigated. The osseous components were in all cases too small with respect to gestational age

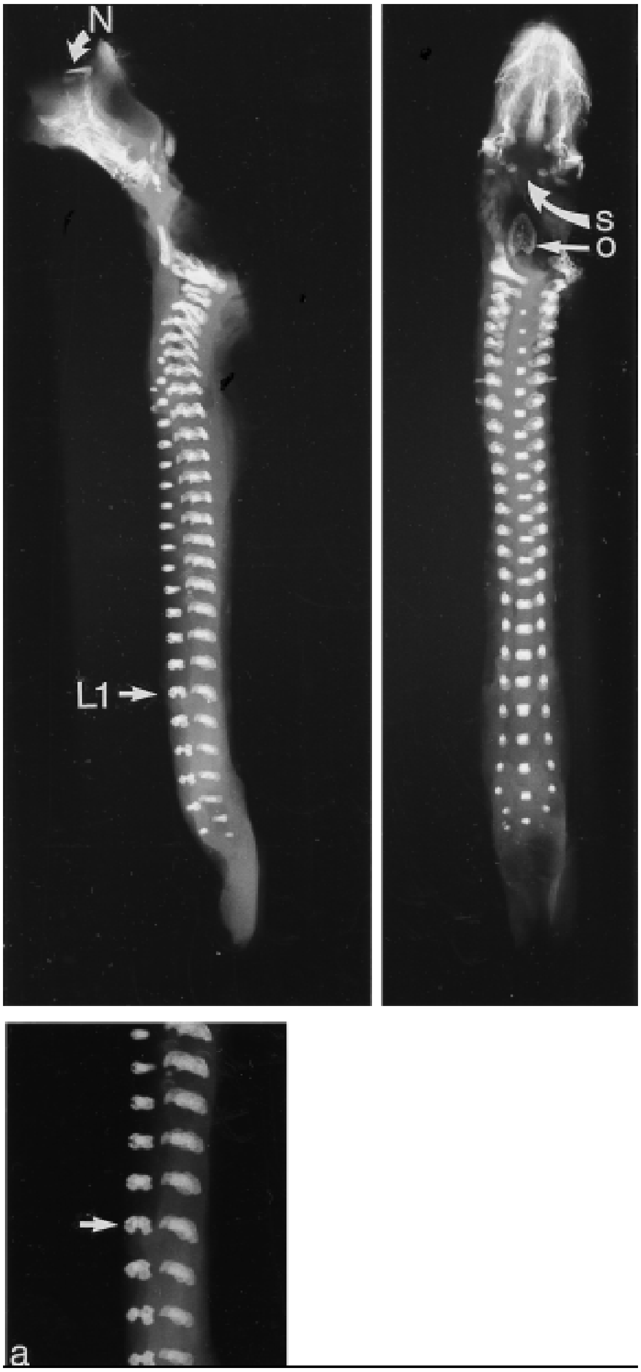

Fig. 2. Radiograph of the axial skeleton in lateral projection (left) and in frontal projection (right) of a human trisomy 13 fetus, gestational age 18 weeks, ×1.2. On the lateral radiograph, N indicates the nasal bone, and L1 the first lumbar vertebral body. L1 is cleft. On the frontal radiograph, O indicates the basilar part of the occipital bone, which has a normal morphology, and S indicates the posterior part of the body of the sphenoid bone. S is malformed, with bilateral ossification centres. **a:** Magnification of the vertebral column in lateral projection in the region around the first lumbar vertebra (arrow). The bodies of the first, third and fourth lumbar vertebrae are partly cleft.

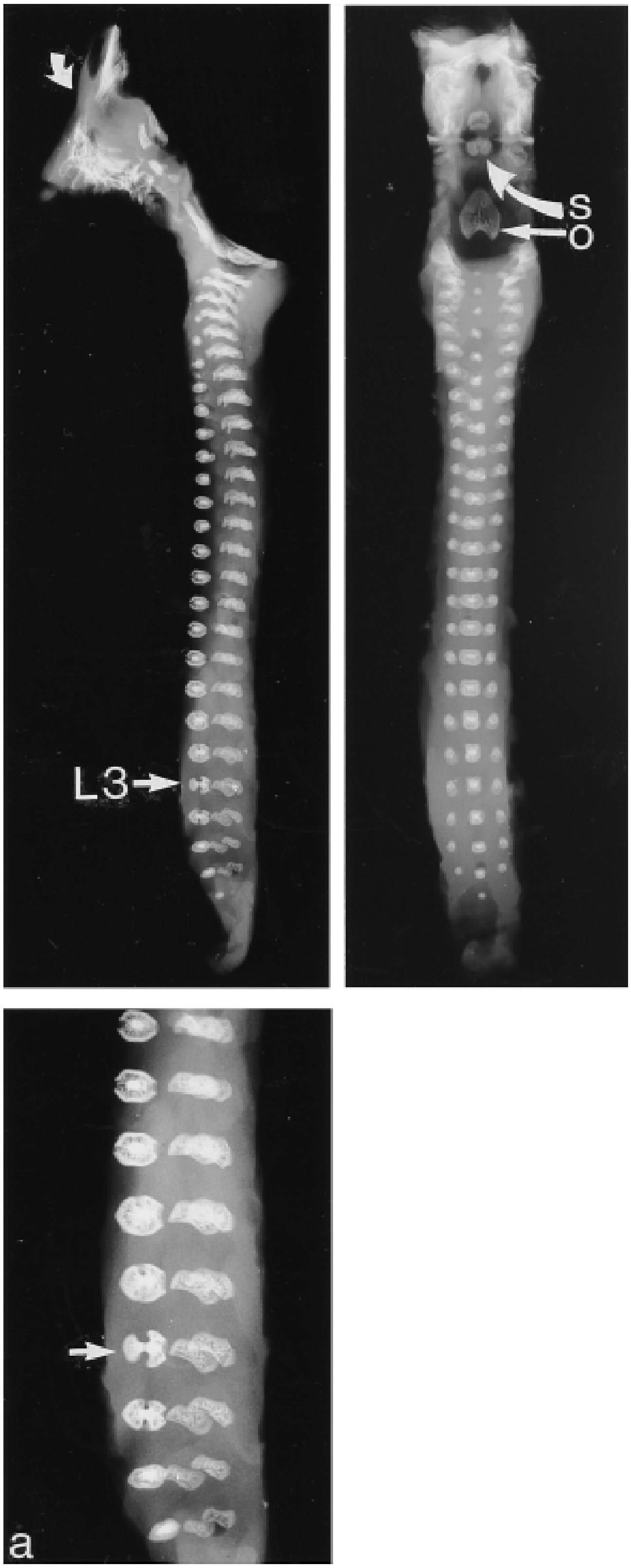

Fig. 3. Radiograph of the axial skeleton in lateral projection (left) and in frontal projection (right) of a human trisomy 13 fetus, gestational age 19 weeks, ×1. On the lateral radiograph the curved arrow indicates the normal location of the nasal bone, which is absent. On the lateral radiograph, L3 indicates the third lumbar vertebral body, which appears partly cleft. On the frontal radiograph, O indicates the basilar part of the occipital bone, which is normal, and S indicates the posterior part of the body of the sphenoid bone. S appears with two separate ossification centres. **a:** An enlarged section of the vertebral column in lateral projection in the region around the third lumbar vertebra (arrow). The lumbar bodies of the third and fourth lumbar vertebrae appear partly cleft.

Fig. 4. Whole body radiograph in lateral projection of a human trisomy 13 fetus, gestational age 19 weeks. ×0.6. N indicates the nasal bone and L3 marks the lumbar vertebral body. **a:** Enlarged section of the vertebral column in the region around the third lumbar vertebra (arrow). The third lumbar body is partly cleft and malformed, and the first lumbar body has a minor partial clefting.

and abnormally configured compared to the normal postsphenoid bone morphology and location as illustrated in Figure 1. The type of malformation seen in five cases was faint bilateral ossification centres (Fig. 2), and in one case two ossification centres in the midaxial plane (Fig. 3).

Nasal Bones

Agenesis of nasal bones occurred in six of eight fetuses (Figs. 3, 5). The term agenesis was used when the bone was not visible at the age at which it should normally have been visible.

DISCUSSION

There are few systematic studies of trisomy fetuses and most are of small numbers of cases [Marin-Padilla et al., 1964; Butler et al., 1973; Greenberg et al., 1983; Nakazato et al., 1985; McKeown and Donnai, 1986; Fujinaga et al., 1990]. The structures and organs that have been studied in detail are eye changes, cleft lip and palate, cardiac defects, polydactyly, renal changes, and brain malformations.

The 2nd trimester axial skeleton in fetuses with trisomy 13 was not studied previously, although such studies were made in trisomy 18 and trisomy 21 [Kjær et al., 1996; Keeling et al., 1997]. Axial skeletal analysis in trisomy 13 demonstrates characteristic abnormalities in the lumbosacral spine, sphenoid, and nasal bones. Comparison of the findings of the present study with the axial skeletal abnormalities in trisomy 18 and 21 shows that the pattern of malformation was different. For instance, the lumbosacral region was always abnormal in trisomy 13, frequently abnormal in trisomy 18, and seldom in trisomy 21 (8 out of 31 fetuses). In contrast, the cervical region was very often malformed in trisomy 21, rarely malformed in trisomy 18, and normal in trisomy 13.

Also there were marked differences in the cranial base. For instance, the basilar part of the occipital bone was always malformed in trisomy 18 but this was not observed in trisomy 13, while malformations in this region were rare in trisomy 21 (1 out of 31 fetuses).

Many trisomy 13 fetuses have holoprosencephaly. In an earlier study of craniofacial development in eight human fetuses with holoprosencephaly with varying phenotypic appearance [Kjær et al., 1991], there proved to be a remarkable correspondence between the type of facial malformation and the extent of the skeletal malformations in the craniofacial skeleton. In a subsequent study of two fetuses with holoprosencephaly the sella turcica was found to be malformed and the adenohypophysis was partly located in the pharyngeal submucosa [Kjær and Fischer Hansen, 1995b]. In the present study of 8 trisomy 13 fetuses, 5

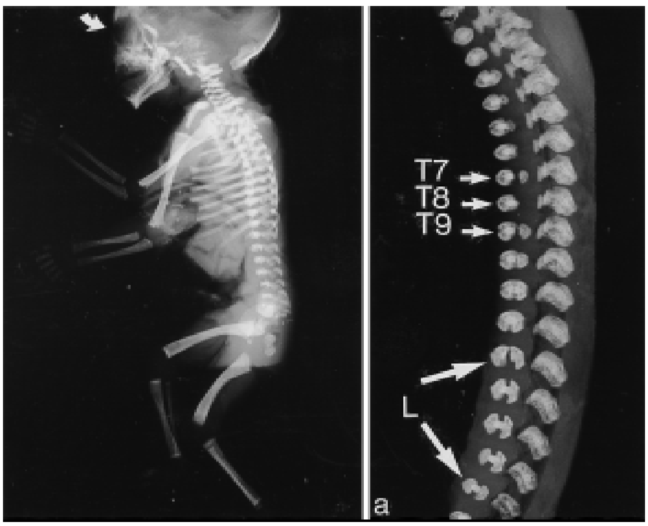

Fig. 5. Whole body radiograph in lateral projection (left) of a human trisomy 13 fetus, gestational age 19 weeks, ×0.4. The arrow indicates the normal location of the nasal bone, which is absent. **a:** Radiograph of the thoracic and lumbar vertebrae in lateral projection after dissection of the axial skeleton, shown left ×1.4 compared to original size. All five lumbar bodies marked L are partly cleft or malformed. Several of the thoracic bodies are malformed, including T7, T8, and T9. Complete vertical clefting of T7 and T9 is seen. In T8 only the anterior part of the vertebral body is ossified.

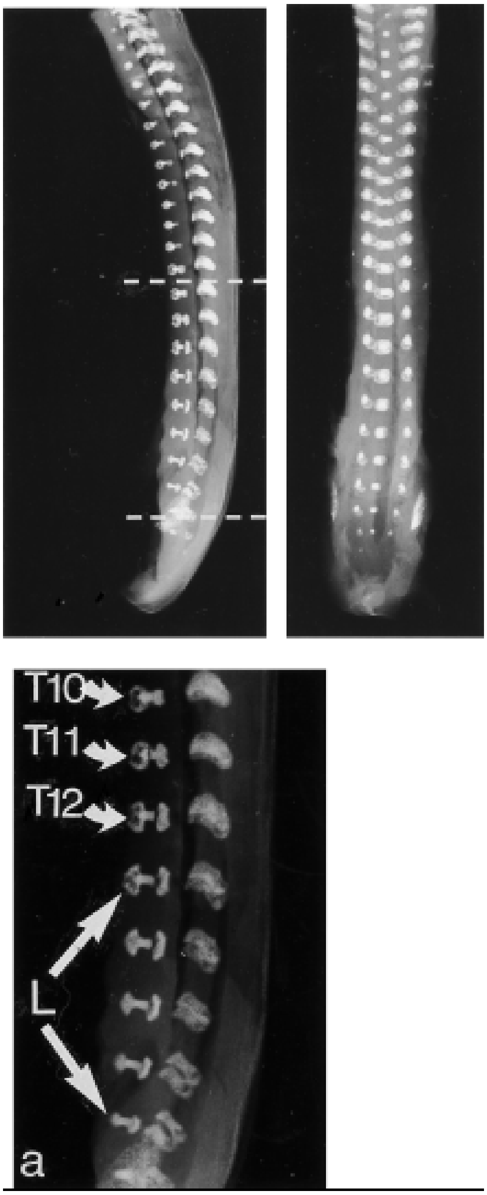

Fig. 6. Radiograph of the vertebral column of the axial skeleton in lateral projection (left) and in frontal projection (right) of a human trisomy 13 fetus, gestational age 18 weeks. ×1. The segment of the vertebral column between the dotted lines includes the lumbar field. There are malformations of all lumbar vertebral bodies. **a:** Enlargement of the marked segment of the vertebral column, ×2. There is partial clefting of all the vertebral bodies.

of which had holoprosencephaly, it is interesting to note that the craniofacial development in the fields anterior to the sella turcica was similarly malformed, and in addition malformations occurred in the lumbosacral segment of the vertebral column. The relationship between the type and extent of malformation in these different developmental fields merits examination.

Our studies have shown that the axial skeleton shows characteristic malformations in three autosomal trisomy syndromes. Radiographic studies of the axial skeleton in the second trimester may contribute to a diagnosis, particularly when chromosome examination was not done or was unsuccessful as, for example, in

TABLE I. Number of Malformed Vertebral Bodies in the Lumbosacral and Thoracic Spine in Six Human Trisomy 13 Fetuses*

Fetus, age	Lumbosacral spine	Thoracic spine	Illustration (Fig.)
18wGA	4	0	(2)
19xGA	3	0	(3)
17wGA	4	7	—
18wGA	5	9	(5)
19wGA	5	9	—
17wGA	5	12	(6)

*The table shows that there is an apparent correspondence between the number of malformed vertebral bodies in the lumbosacral spine and the number of malformed vertebral bodies in the thoracic spine.

intrauterine death or spontaneous abortion [Kjær, 1994; Kjær and Fischer Hansen, 1995a]. Similarly, when dissection is not permitted, a whole body radiograph may disclose the skeletal abnormalities of the lumbar and nasal regions. In other regions overlap of bony contours makes the interpretation of the axial structures difficult. We have also shown that skeletal analysis is useful in distinguishing between anencephaly and amnion rupture sequence with cranial involvement [Keeling and Kjær, 1994].

Analysis of the axial skeleton seems to demonstrate phenotypic characteristics in the three trisomy genotypes examined so far. Since characteristic morphological abnormalities in the axial skeleton were also found in anencephaly [Kjær et al., 1994], in spina bifida, and in encephalocele [Kjær et al., 1996], it is likely that the axial skeleton, which is formed around the notochord in the second trimester, exhibits a phenotypic expression of a genotypic abnormality. Systematic analysis of the axial skeleton in a range of malformation syndromes with known and, as yet, unknown genetic abnormalities is essential. The prospect of skeletal analysis in fetuses with more precisely defined chromosome abnormalities is exciting.

Finally, the study shows that analysis of the whole axial skeleton in fetuses with the same genotype might provide information about the relationship between the development of the spine and of the cranial base.

REFERENCES

Butler LJ, Resis HE, France NE, Briddon S (1973): Antenatal diagnosis of Patau's syndrome (trisomy 13) including a detailed pathological study of the fetus. J Med Genet 10:367–370.

Colacino SC, Pettersen JC (1978): Analysis of the gross anatomical variations found in four cases of trisomy 13. Am J Med Genet 2:31–50.

Fujinaga M, Shepard TH, Fitzsimmons J (1990): Trisomy 13 in the fetus. Teratology 41:233–238.

Gilbert EF, Opitz JM (1982): Developmental and other pathologic changes in syndromes caused by chromosome abnormalities. Perspect Pediatr Pathol 7:1–63.

Greenberg F, Carpenter RJ, Ledbetter DH (1983): Cystic hygroma and hydrops fetalis in a fetus with trisomy 13. Clin Genet 24:389–391.

Jacobs PA, Hassold TJ, Henry A, Pettay D, Takaesu N (1987): Trisomy 13 ascertained in a survey of spontaneous abortions. J Med Genet 24:721–724.

Keeling JW (1994): "Fetal Pathology." London: Churchill, Livingstone, pp 20–23.

Keeling JW, Kjær I (1994): Diagnostic distinction between anencephaly and amnion rupture sequence based on skeletal analysis. J Med Genet 31:823–829.

Keeling JW, Fischer Hansen B, Kjær I (1997): Pattern of malformations in the axial skeleton in human trisomy 21 fetuses. Am J Med Genet 68: 466–471.

Kjær I (1974): Skeletal maturation of the human fetus assessed radiographically on the basis of ossification sequences in the hand and foot. Am J Phys Anthropol 40:257–276.

Kjær I (1990a): Ossification of the human fetal basicranium. J Craniofac Genet Dev Biol 10:29–38.

Kjær I (1990b): Radiographic determination of prenatal basicranial ossification. J Craniofac Genet Dev Biol 10:113–123.

Kjær I (1994): The prenatal axial skeleton as marker of normal and pathological development of the human central nervous system. In Lou HC, Greisen G, Larsen JF (eds): "Brain Lesions of the Newborn" (Alfred Benzon Symposium #37). Copenhagen: Munksgaard, pp 124–132.

Kjær I, Fischer Hansen B (1995a): Postmortem axial skeletal radiography can reveal fetal CNS malformation. APMIS 103:574–581.

Kjær I, Fischer Hansen B (1995b): Human fetal pituitary gland in holoprosencephaly and anencephaly. J Craniofac Genet Dev Biol 15:222–229.

Kjær I, Keeling JW, Fischer Hansen B (1996): Pattern of malformations in the axial skeleton in human trisomy 18 fetuses. Am J Med Genet. 65:332–336.

Kjær I, Fischer Hansen B, Keeling JW (1996): The axial skeleton and the pituitary gland in human fetuses with spina bifida and cranial encephalocele. Pediatr Pathol 16:909–926.

Kjær I, Keeling JW, Græm N (1991): The midline craniofacial skeleton in holoprosencephalic fetuses. J Med Genet 28:846–855.

Kjær I, Keeling JW, Græm N (1994): Cranial base and vertebral column in human anencephalic fetuses. J Craniofac Genet Dev Biol 14:235–244.

Kjær I, Kjær TW, Græm N (1993): Ossification sequence of occipital bones and vertebrae in human fetuses. J Craniofac Genet Dev Biol 13:83–88.

Kyrkanides S, Kjær I, Fischer Hansen B (1993): Development of the basilar part of the occipital bone in normal human fetuses. J Craniofac Genet Dev Biol 13:184–192.

Marin-Padilla M, Hoefnagel D, Benirschke K (1964): Anatomic and histpathologic study of two cases of D1 (13–15) trisomy. Cytogenesis 3:258–284.

McKeown CME, Donnai D (1986): Prune belly in trisomy 13. Prenat Diagn 6:379–381.

Mottet NK, Jensen H (1965): The anomalous embryonic development associated with trisomy 13–15. Am J Clin Pathol 43:334–347.

Nakazato Y, Gilsanz V, Falk RE (1985): Fetal cystic hygroma, web neck and trisomy 13 syndrome. Br J Radiol 58:1011–1013.

Opitz JM, Herrmann J, Pettersen JC, Bersu ET, Colacino SC (1979): Terminological, diagnostic, nosological, and anatomical developmental aspects of developmental defects in man. In "Advances in Human Genetics." New York: Plenum Press, pp 71–165.

Patau K, Smith DW, Therman E, Inhorn SL, Wagner HP (1960): Multiple congenital anomaly caused by an extra autosome. Lancet I:790–793.

Pettersen JC, Koltis GG, White MJ (1979): An examination of the spectrum of anatomic defects and variations found in eight cases of trisomy 13. Am J Med Genet 3:183–210.

Sandickioglu M, Mølsted K, Kjær I (1994): The prenatal development of the human nasal and vomeral bones. J Craniofac Genet Dev Biol 14:124–134.

Snodgrass GJAI, Butler LJ, France NE, Crome L, Russell A (1966): The "D" (13–15) trisomy syndrome: An analysis of 7 examples. Arch Dis Childh 41:250–261.

Taylor AI (1968): Autosomal trisomy syndromes: A detailed study of 27 cases of Edward's syndrome and 27 cases of Patau's syndrome. J Med Genet 5:227–252.